HIGH SENSITIVITY C – REACTIVE PROTEIN AS A DETERMINANT IN THE OUTCOME OF ACUTE ISCHEMIC STROKE

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BONAFIDE CERTIFICATE

This is to certify that "**HIGH SENSITIVITY C – REACTIVE PROTEIN AS A DETERMINANT IN THE OUTCOME OF ACUTE ISCHEMIC STROKE**" is bonafide work done by **Dr. D. Radha,** post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D.Degree Branch I (General Medicine)** during the academic period from May 2006 to March 2009.

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ETHICAL COMMITTEE OF
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KILPAUK, CHENNAI-10.
Venue: Dean Chamber, Date: 3.1.2008

Chair person
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TO WHOMSOEVER IT MAY CONCERN

Dear Sir / Madam

Sub: Internal Medicine – MD PG's Dissertation Ethical Committee – Reg.

Ref: Requisition from H.O.D. Medicine.

This is in reference to the letter dated 2.1.2008 regarding Ethical committee meeting clearance with regard to the following topics

Sl.No	Name of the Post Graduate	Dissertation Topic
1	Dr. R.Ramprasad	A study on Prevalence and Risk Factors of Diabetic Nephropathy in Newly Detected Type 2 Diabetic Patients
2	Dr. V.Sakthivadivel	A study on Cardiac abnormalities in HIV infected individuals
3	Dr. K.S.Gopakumar	A study on Subclinical Hypothyroidism in females over 50 years of age
4	Dr. T.Karthikeyan	Inflammatory profile in Acute Myocardial Infarction

5	Dr. Maliyappa Vijay Kumar	A study on Prevalence of Microalbuminuria in HIV patients not on ART and Correlation with CD4 count
6	Dr. D.Radha	High sensitivity C - reactive protein as a determinant in the outcome of Acute ischemic stroke
7	Dr. Lakshmi Thampy M.S	A Study on the prevalence of increased LV mass & Proteinuria in newly diagnosed Hypertensive patients.
8	Dr. Manu Bhasker	A study on the effect of Intravenous Metoprolol along with Thrombolysis in Acute Myocardial infarction
9	Dr. P.Mohanraj	Evaluation of Lipid Profile in patients with non diabetic Chronic Kidney Disease Stage 3,4 and 5
10	Dr. P.Dhanalakshmi	A study On Metabolic Syndrome in Young Ischemic Stroke
11	Dr. V.Murugesan	A study on Electrocardiographic and Echocardiographic changes in Chronic Obstructive Airway Disease
12	Dr. M.Seetha	Effect of Right ventricular infarction on the immediate prognosis of Inferior wall Myocardial Infarction

We are glad to inform you that at the EC meeting held on 3.1.08 on the above topics were discussed and **Ethically approved**.

DEAN

Chair person
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Chairman & Members of the Ethical Committee:

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   Nursing Superintendent

We confirm that no member of the study team is on the Ethics Committee and no member of the study team voted.

The trial will also follow the Ethics Guidelines for Bio-Medical Research On Human subjects issued by ICMR, New Delhi and will not involve any expense to the Government and will not be detrimental to the normal functioning of the Institution.

The study will also satisfy the revised order issued by the Government of Tamil Nadu, Health and Family Welfare Department G.O.MS.No:319, H & FW, Dept. dated 30.11.2001.

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CONTENTS

INTRODUCTION

In recent years, there has been increasing evidence which shows strong links between inflammation and the pathogenesis of atherothrombotic stroke. Acute phase proteins have been implicated to play roles both during acute and chronic inflammatory processes in different diseases including ischemic stroke[1]. Even low grade infections may cause elevation of various acute phase reactants which may partly be responsible for the inflammatory process observed in atherosclerotic lesions, which may inturn relate to occurrence of ischemic symptoms[2].

Inflammation plays a major role in atherothrombosis and measurement of inflammatory markers such as C–Reactive Protein, an acute phase reactant that reflects low-grade systemic inflammation has been studied in a variety of cardiovascular diseases[3]. There is growing evidence of the prognostic importance of CRP in ischemic stroke[4]. Also CRP has been found to be a strong but relatively non-specific risk factor of fatal stroke in elderly persons[5].

CRP, a sensitive meter of inflammation, induces vascular thrombosis by stimulating monocytes to express tissue factor, the initiator of the extrinsic pathway of coagulation[6]. Elevated levels of CRP are found to be related with

higher risk of first-ever cardiovascular, cerebrovascular and peripheral vascular diseases[7].

The WHO has recently set international reference standard for the use of highly sensitive CRP assays. This has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events.

AIM

1. To evaluate the predictive value of hs-CRP in relation to the ultimate functional outcome in first ever ischemic stroke after 4 weeks.

2. To correlate the hs-CRP levels with various cardiovascular risk factors.

REVIEW OF LITERATURE

Stroke:

Stroke or cerebrovascular accident is defined as a rapidly developing clinical symptoms and or signs of focal and at times global (applied to patients in deep coma) loss of cerebral function with symptoms lasting more than 48 hours or leading to death with no apparent cause other than that of vascular origin.

Table 1: Pathologic Classification of Stroke

Pathologic type[8]	Percentage (%)
Cerebral Infraction ▪ Large vessel occlusion ▪ Small vessel occlusion ▪ Cardiac emboli ▪ Hematological disorders	80%
Primary intracerebral hemorrhage ▪ Hypertensive bleeding ▪ Vascular malformations ▪ Bleeding diathesis ▪ Anticoagulants	10%
Non traumatic SAH ▪ Aneurysm ▪ Vascular malformation ▪ Non-aneurysmal SAH	5%
Other causes	5%

CAUSES OF CEREBRAL ISCHEMIA AND INFARCTION[9]

- Arterial Wall disorder
- Atherthromboembolism
- Intracranial small vessel disease (lipohyalinosis, microatheroma),
- Trauma
- Dissection
- Fibromuscular dysplasia
- Congenital arterial anomalies
- Moya Moya syndrome
- Embolism from arterial aneurysm
- Inflammatory vascular disease
- Binswanger disease
- Irradiation, infection
- Embolism from the heart
- Hematological disorders
- Miscellaneous:

    Pregnancy

    OCP

    Drug Abuse

    Cancer

    Migraine

Inflammatory Bowel Disease

Homocystinemia

Fabry's disease

Mitochondrial Cytopathy

Hypercalcemia

Hypoglycemia

Epidermal nevus syndrome

Fat embolism

Thus it is evident that

1) Cerebral infraction accounts for 80% of all strokes.
2) Atherothromboembolism of cerebral arterial supply is the cause in about 50% of the cases of cerebral infarction

ATHEROSCLEROSIS

Atherosclerosis is a disease primarily of the elastic arteries (eg:aorta, carotid, iliac arteries) large and medium sized muscular arteries (eg:coronary and popliteal arteries). Laboratory and clinical evidence has demonstrated that atherosclerosis is not simply a disease of lipid deposits. Rather, systemic inflammation also plays a pivotal role in atherothrombotic inception and progression[10,11,12]. Mononuclear cells, macrophages, and T lymphocytes are prominent in atheromatous plaques in the arterial wall[13,14,15,16]. Furthermore,

the shoulder region of a plaque, the most vulnerable site for rupture in acute coronary syndromes, is heavily infiltrated with inflammatory cells[17,18,19]. Cytokines, which cause the de novo hepatic production of acute phase reactants such as C-reactive protein[20], have been shown to increase in acute coronary syndromes even in the absence of myocardial necrosis[21]. Therefore, CRP has been examined as a surrogate marker of other inflammatory mediators such as interleukin-6 and tumor necrosis factor-α to understand better the inflammatory component of atherosclerosis[22,23]. Current knowledge, however, suggests that the CRP concentration might reflect the vulnerability of the atheromatous lesion and the likelihood of a plaque to rupture[11,12,24]. This acute phase reactant has been studied over the last several years in a wide variety of atherosclerotic diseases[21,25,26,27,28,29]. Its prognostic utility in acute coronary syndromes[21,25,26,27,28,29] and its ability to predict future coronary events in apparently healthy men and women[30,31,32,33,34,35,36,37,38,39] have been demonstrated. The development of high sensitivity CRP (hs-CRP) assays has been instrumental in exploration of the role of this acute phase reactant in predicting first cardiovascular and cerebrovascular events.

RISK FACTORS FOR STROKE

Since stroke is a multifactorial disease, both genetic and environmental risks affect the disease.

1. Age and gender:

Stroke incidence increases with age. With each decade after 55 years, the risk doubles. Approximately 80% of strokes occur in the elderly. Gender also affects the risks. Men develop strokes at a higher rate than women up to the age of 75[40].

2. Smoking:

Cigarette smoking is a well established risk factor for ischemic stroke[41,42]. A meta-analysis has shown a 50% increase in stroke risk for smokers[43].

3. Diabetes Mellitus:

Diabetes mellitus increases stroke risk to 2 to 4 fold compared to non-diabetes subjects while also increasing mortality and morbidity after stroke.

4. Hypertension:

Hypertension is the single most important modifiable risk factor for all strokes accounting for up to 50% of all strokes[44].

5. Hypercholestrolemia:

Both elevated total cholesterol as well as low density lipoprotein increases the risk of CHD and stroke.

6. Homocysteinemia:

Homocysteinemia has been described as a possible risk factor for ischemic stroke. Presumed mechanism is increased stress tolerance of the endothelium, thrombosis, inflammation and oxidative stress[45].

7. Inflammation and bio-markers:

Inflammation as part of atherosclerotic pathway has been implicated in cardiovascular disease and ischemic stroke. Inflammatory biomarkers such as CRP, IL-6 and heat shock proteins have been shown to be elevated in acute ischemic stroke[46,47,48,49,50,51,52,53].

8. Evidence of existing vascular disease:

Myocardial infarction
Cardiac failure
Atrial fibrillation
Peripheral vascular disease
Transient ischemic attacks
Carotid arterial bruit and stenosis

9. Miscellaneous[9,54] :

Plasma fibrinogen

OCP

Alcohol

PREDICTORS OF STROKE OUTCOME

I) Demographic factors:

1. Age:

Age is one of the major factors that negatively influence the outcome for patients with ischemic stroke[55]. Older patients are less likely to recover than younger patients with similar sized infarcts.

2. Gender:

Some studies have shown male sex associated with poorer outcome[56] whereas other studies have shown no difference. The explanation for this may be hormonal. Estrogen seems to be an important mediator of improved outcome after ischemic brain injury.

3. Race/Ethnicity:

Although it is well understood that the incidence of stroke varies among races and ethnicities, there is no significant difference in the outcome between groups[57].

II) Cerebrovascular risk factors:

1. Previous stroke and atrial fibrillation:

Strokes in patients with previous stroke and atrial fibrillation are usually more severe, more disabling and associated with a higher moratlity.

III) Clinical findings:

1. Level of consciousness and gaze deviation:

Initial level of consciousness is an important predictor with decreased level of consciousness predicting poor outcome[58]. The presence of gaze deviation is associated with poor outcome.

2. Blood Pressure:

Abnormal blood pressure may influence outcome. Clinical studies of blood pressure reduction have shown a decrease in cerebral blood flow to the infracted area[59]. On the contrary, excessively elevated blood pressure has negative long term effects on blood brain barrier function.

3. Temperature:

For each one degree celsius increase in body temperature, the relative risk of poor outcome rises two fold[60]. This may be due to the increased concentration of excitotoxic neurotransmitters present. Elevated temperature

(>37.5^{0}C) was an independent predictor of large volume infarct and higher neurological deficit when it occurred in the first 24 hours after first stroke onset.

IV) Laboratory findings:

1. Glycine and glutamate:

High glycine or glutamate levels strongly correlated with large infarct size and severe neurological deficits[61].

2. S-100:

Increased serum levels of S-100 correlate with neurologic outcome.

3. Neuron-specific enolase:

This enzyme has been shown to increase in acute stroke.

4. Serum Glucose:

Hyperglycemia is associated with increased morbidity and mortality[62]. Hyperglycemia seems to produce its detrimental effects by causing a profound cellular acidosis. Clinical studies have shown an association between hyperglycemia and cerebral edema[62].

PROGNOSTIC VALUE OF ACUTE PHASE REACTANTS (APR)

1. Erythrocyte Sedimentation rate (ESR):

Elevated ESR predicts poor outcome[63].

2. C-reactive protein (CRP):

CRP concentrations measured within 72 hours of stroke independently predicted survival after ischemic stroke. Patients with levels above 10.1 mg/L had significantly worst survival[64].

C REACTIVE PROTEIN

History and nomenclature:

CRP was originally discovered by Tillet and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with C-polysaccharide of Pneumococcus[65]. It is a 23- KDa protein[65].

Genetics and Biochemistry:

The CRP gene is located on the first chromosome (1q21-q23).CRP is a 224 residue protein with a monomer molar mass of 25106 Da and native cyclic pentamer mass of 125530.

Function:

CRP is a member of the class of acute phase reactants. It is thought to assist in complement binding to foreign and damaged cells and affect the humoral response to disease. It is believed to play an important role in innate immunity, as an early defense system against infection.

Diagnostic Use:

CRP is used mainly as a marker of inflammation. Measuring and charting CRP values can prove useful in determining disease processes or the effectiveness of treatment.

CRP and Atherosclerosis:

Accumulating data suggest that arterial tissues can produce CRP, with CRP and complement m-RNA being substantially upregulated in atherosclerotic plaque[11]. Thus CRP may serve as an endogenous activator of complement in atheroma.

Dynamics of CRP:

The acute phase response comprises the non-specific physiological and biochemical responses of endothermic animals to most forms of tissue

damage, infection, inflammation and neoplasia. In particular the synthesis of a number of protein is upregulated principally in hepatocytes under the control of a cascade of cytokines, including interleukin-1, tumour necrosis factor-α and interleukin-6 originating at the site of pathology.

CRP levels rapidly rise after an inflammatory stimulus and depending on the intensity of the stimulus, even as several 100 fold increase in plasma levels may occur[66]. CRP is not consumed to a significant extent in any process and its clearance is not influenced by any known condition. Therefore its concentration appears to be dependent on the rates of production and excretion. The long half life of CRP approximately 19 hours, makes it's detection in blood easy even several hours after acute stimulus. Because of all these characters, CRP can be called as an “ideal marker of inflammation”.

CRP VS OTHER ACUTE PHASE PROTEINS

The group of acute phase proteins includes, besides CRP, many other proteins, such as Serum Amyloid A (SAA), fibrinogen, pro-calcitonin, haptoglobin, alpha 2 haptoglobin, alpha 1 acid glycoprotein, ceruloplasmin, alpha 1 anti-trypsin and albumin.

The disadvantage of haptoglobin, alpha 2 haptoglobin, alpha 1 acid glycoprotein, ceruloplasmin, alpha 1 anti-trypsin and albumin is that the

difference between normal and pathological values are very small. The values measured in pathological conditions are only a few times those found in healthy individuals, and they are also determined by other (ex: nutrional) factors in addition to infections.

Determination of SAA is totally cumbersome because of lack of methods for routine measurements. Compared to many other acute phase proteins, CRP has the advantage that pathological values are easy to detect since the increase in concentration can be several 100 fold.

Hepatocyte CRP is triggered by cytokines such as IL-1, IL-6 and tumour necrosis factor secreted by monocytes, macrophages. The elevation of IL-6 concentration in serum is one of the earliest markers of inflammatory processes, detectable 2 to 3 hours after onset of infection. Similarly IL-6 concentration is normally detectable 4 to 7 hours later depending on the sensitivity of the assay.

HIGH SENSITIVITY CRP (hs-CRP)

In the late 1990s, high sensitivity CRP assays became available, allowing assessment of serum concentrations at the lower end of its distribution. In the subsequent years, hs-CRP levels far beneath the cutoff value, indicative of an immediate-phase response, predicted the risk of

cardiovascular, cerebrovascular disease, diabetes mellitus, and cognitive impairement [67,68,69,70].

Normal reference range: 0.02 to 8.0 mg/L

ROLE OF ACUTE PHASE REACTANTS IN ACUTE ISCHEMIC STROKE

Inflammatory factors play an important role in the pathogenesis of ischemic stroke. Acute phase proteins level such as a fibrinogen, CRP, ferritin increase after acute ischemic stroke. These findings support a possible role of an inflammatory stimulus in the acute ischemic stroke.

Fibrinogen:

In acute phase of cerebrovascular diseases, biochemical markers of inflammation could be useful to predict severity of stroke[71]. Fibrinogen is a well known acute phase protein and risk factor for myocardial infarction and stroke. High fibrinogen levels represent an acute phase response in early acute stroke[72].

Fibrinogen is involved in primary haemostasis, platelet aggregation, and leukocyte-endothelial cell interactions and is the major determinant of

whole blood and plasma viscosity[73]. Fibrinogen levels increase after an acute stroke [74].

Ferritin:

There are some evidences about the significant role of iron (Fe^{+2}) in cerebral damage[75]. The role of iron in acute ischemic stroke has been investigated; as a result of this research, there may be relationship between high iron level and poor prognosis[74].

It is suggested that high serum ferritin levels within the first day of hospitalization for an acute ischemic stroke are related to poor prognosis[75]. Oxidative metabolism during ischemic stroke together with high iron content in the brain synergise to increase the oxidative damage. High plasma ferritin, as a measurement of iron stores, and high cerebrospinal fluid ferritin have been related to poor outcome in stroke patients[76]. Serum ferritin level and large size of lesion were independently associated with mortality. Increased serum ferritin levels correlate to severity of stroke and the size of the lesion[77].

CRP:

High levels of hs-CRP are associated with adverse cardiovascular and cerebrovascular events. High CRP predicts the risk of carotid stenosis; first stroke and post stroke mortality.

CRP AND CORONARY EVENTS

In patients with established coronary disease, CRP has been shown to predict adverse clinical events. In addition, prospective studies have consistently shown that CRP is a strong predictor of future coronary events in apparently healthy men and women. The relative risk associated with CRP is independent of other cardiovascular disease risk factors. High sensitivity CRP (hs-CRP) assays are needed for risk assessment of cardiovascular disease.

CRP AND ISCHEMIC STROKE

Elevated plasma CRP concentrations are also associated with an increased risk of cerebrovascular events and an increased risk of fatal and nonfatal cardiovascular events in ischemic stroke patients[78]. Determination of plasma CRP concentrations could be used as an adjunct for risk assessment in primary and secondary prevention of cerebrovascular disease and be of prognostic value. CRP is as an independent predictor of cerebrovascular events in at-risk individuals and ischemic stroke patients.

FRAMINGHAM STUDY:

To address the baseline CRP level and the risk of subsequent stroke events, the measurement of CRP was done in the Framingham study original

cohort who were free of stroke or TIA at the time of their 1980 to 1982 clinical examination and related the baseline CRP plasma generation to the incidence of first stroke or TIA in these subjects during a 12 to 14 years follow up – men with the higher baseline CRP values had twice the risk of ischemic stroke and women with highest CRP level had a 5-fold increase in risk of any vascular event and a 7-fold increase in risk of the comorbid outcome of myocardial infarction or stroke. The data derived from this study demonstrated a graded increase in the incidence of ischemic stroke and TIA with increased levels of CRP[79].

RELATIONS OF hs-CRP TO VARIOUS CARDIOVASCULAR RISK FACTORS

There is increasing evidence that higher levels of hs-CRP is a predictor of cardiovascular disease (CVD), and may play an important role in the different stages of the development of atherosclerosis[3,38].

In healthy subjects even a moderate increase of hs-CRP within the normal range (hs-CRP <5 mg/L) is considered to be predictive for a variety of cardiovascular events, independent from other cardiovascular risk factors[3,38,80].

Increased CRP levels showed statistically significant positive correlations with other established risk factors including age, number of cigarettes smoked per day, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, homocysteine, fibrinogen, and D-dimers; CRP levels are correlated inversely with exercise frequency and high density lipoprotein cholesterol (HDL-C)[81]. CRP has emerged as a strong, independent risk factor in its own right.

A study was performed by So Yeon Ryu and his colleagues to evaluate the relation of high sensitivity C-reactive protein with several cardiovascular risk factors such as age, blood pressure, smoking habit and serum lipids, body mass index, blood glucose, regular exercise, alcohol drinking, white blood cell counts in a cross-sectional survey[82]. Plasma hs-CRP was measured by immunoturbidimetry in 202 subjects, aged over 50 years, who participated in health-check survey in a rural area of Jeollanamdo, Korea. Plasma hs-CRP level was 1.9 ± 3.0 mg/dL. He concluded that there were significant associations between hs-CRP levels and age, white blood cell counts, blood glucose, diastolic blood pressure, HDL-cholesterol, body mass index and smoking status. Although the correlation between plasma hs-CRP and HDL-cholesterol was negatively significant, other blood lipid profile, such as total cholesterol, triglyceride and LDL-cholesterol did not significantly correlate

with hs-CRP. Smoking is well supposed to give chemical and oxidative stimuli to the cardiovascular system and cause inflammation[83]. It has recently been reported that moderate alcohol consumptions reduces circulating CRP[84]. But in his study, the plasma hs-CRP level was not significantly affected by the alcohol drinking.

Increased intima-media thickness of the common carotid arteries and elevated levels of hs-CRP are both shown to be associated with the occurrence of stroke[85]. This was shown in a study conducted by Gulcin Benbir and his colleagues. He studied the relationship of elevated hs-CRP levels with the extent of carotid atherosclerosis . He studied 104 patients aged between 30 to 92 yrs with acute ischemic stoke. The hs-CRP determination was performed within 72 hours after admission. The relationship between the hs-CRP level and the other risk factors were also evaluated in his study. All of the variables except HDL levels, failed to show a significant relationship with the hs-CRP levels. Only variable that showed a significant relation with the levels of the hs-CRP was HDL levels. It was shown that the major risk factors of the stroke were also associated with the higher levels of CRP[83] and the treatment with antiaggregants and statins might have lowered the levels of CRP through their regulatory effects on the inflammation[86,87].

High blood pressure, as well as triglycerides, HDL cholesterol and diabetes were found to be strongly associated with CRP in a study by Blackburn R. *et al.,* (2001)[88].

In a study by Choi H. *et al.*, 2004, there was no association between hs-CRP and carotid atherosclerosis in subjects with hypertension and normotension[89].

Smokers had higher WBC, fibrinogen, and CRP levels in a study by Magyar *et al.* (2003)[90]. Several CHD risk factors appear to modulate the inflammatory response and affect hs-CRP concentration. Cigarette smoking has also been shown to increase the concentration of several inflammatory markers, including hs-CRP, interleukin-6, and soluble intercellular adhesion molecule-1[3]. Increases of both interleukin-6 and soluble intercellular adhesion molecule-1 were shown to be associated with increased risk of future first coronary events in both men and women. Smoking cessation decreases these markers.

Diabetic patients are reported to have increased hs-CRP values[91]; In this regard, links between hs-CRP and the insulin resistance syndrome have also been reported . In addition, experimental findings suggest that increased blood pressure promotes endothelial expression of cytokines and

inflammatory activation[15]. These observations suggest that perhaps better control of diabetes and hypertension may attenuate the contribution of the inflammatory response to overall cardiovascular risk. Taken together, the available evidence thus supports the hypothesis that hs-CRP concentrations correlate with endothelial dysfunction .

Also , another study by Liuzzo et al[21] showed that in patients with severe unstable angina, hs-CRP concentrations >3 mg/L at admission were associated with an increased incidence of recurrent angina, coronary revascularization, MI, and cardiovascular death.

In a similar study of unstable angina, Ferreiros et al[27] concluded that the prognostic value of hs-CRP in predicting adverse outcome at 90 days.

A recent report by de Winter et al[26] showed that hs-CRP concentrations >5 mg/L at admission in 150 patients with non-ST-elevation acute coronary syndromes were associated with an increased incidence of major cardiac events within 6 months .

Results from a population-based study in Russia The Arkhangelsk study conducted by M. Averina and his colleagues revealed U-shaped association between hs-CRP and total alcohol intake[92]. This U-shaped

association became non-significant in both sexes after adjustment for age, BMI, smoking status, diabetes mellitus and cardiovascular medication.

Another study conducted by Chrysohoou et al in 2003, showed a U-shaped relation of several biochemical parameters related to atherosclerosis including hs-CRP and the amount of alcoholic beverages consumed[93].

A study by Rasouli Mehdi et al in 2006 , showed that elevated hs-CRP was assosciated with male sex, diabetes, hypertension and high levels of serum glucose[94].

Another study by Minna Soinio et al concluded that diabetic patients have higher levels of hs-CRP than people without diabetes and that elevated hs-CRP levels are an independent risk factor for death from CHD in people with diabetes[95].

PROGNOSTIC INFLUENCE OF CRP LEVELS AFTER FIRST EVER ISCHEMIC STROKE

There is growing evidence of the prognostic importance of C-reactive protein in ischemic stroke. However, the independent value of CRP at different stages after stroke has not been established. Di Napoli and his

colleagues did a study to compare the relation of CRP at admission and discharge with 1-year outcome[96] One hundred ninety-three patients were included in the study. Serum CRP was measured within 24 hours after index ischemic stroke, within 48 to 72 hours, and at hospital discharge. He examined the association between the level of CRP at different stages after stroke and outcome. A cutoff point of 15 mg/L for CRP at discharge provided optimum sensitivity and specificity for adverse outcome, based on the receiver operator curves. He concluded that CRP is a marker of increased 1-year risk in ischemic stroke. CRP at discharge is better related to later outcome and could be of greater utility for risk stratification. These findings are consistent with the hypothesis that elevated CRP may predict future cardiovascular events or death.

Mario Di Napoli and his colleagues also conducted a study on the role of CRP levels in short term prognosis after first ever ischemic stroke. About 30 ischemic stroke patients between the ages of 49 and 90 yrs of age were studied within four weeks of occurrence of the first ever cerebrovascular ischemic events. CRP levels were collected within a media of 14 days from the stroke onset. It was found that patients with the highest CRP levels (> 5mg/L) at study died early or had severe complications after stroke or had no evidence of recovery during the two month follow up[97]. This study

concluded that CRP was increased in patients with cerebral ischemia, the higher levels correlating with significant neurological defecit and disability and appears to provide additional information regarding prognosis after ischemic stroke as it appears to do after myocardial infarction.

Kocer A and his colleagues did a study to evaluate serum hs-CRP levels in ischemic stroke patients and in a control group, and to correlate the values with other generally known risk factors[98]. A total of 47 patients with ischemic stroke and 26 control subjects were recruited. Peripheral blood samples from stroke patients were obtained between 12-24 hours after the stroke. It was found that the mean serum levels of hs-CRP were significantly higher in patients than controls. Also the level of hs-CRP was above the risk limit in 39 patients (83.0%) and 7 controls (26.9%). The hs-CRP values were not related to the presence of other vascular risk factors, except for cholesterol level. In this study the correlation analysis of hs-CRP revealed a linear correlation with death within six months and the presence of hypertension.

Another study conducted by Winbeck K and his colleagues investigated the impact of early serial CRP measurements in hyperacute ischemic stroke on long-term outcome[99]. One hundred twenty-seven consecutive patients without thrombolysis with a first ischemic stroke no

more than 12 hours after symptom onset were examined. Serial CRP measurements were done at admission (CRP 1), within 24 hours (CRP 2), and within 48 hours (CRP 3) after symptom onset. In addition to several cerebrovascular risk factors, the 1-year outcome and the lesion volumes of initial diffusion-weighted images were determined. The CRP level measured within 12 hours after symptom onset of an acute ischemic stroke was not independently related to long-term prognosis. In contrast, a CRP increase between 12 and 24 hours after symptom onset predicted an unfavorable outcome and was associated with an increased incidence of cerebrovascular and cardiovascular events.

Ufuk Emry and his colleagues conducted a study to determine the influence of fibrinogen, CRP and other acute phase reactants in acute ischemic stroke in acute period (first 24 to 72 hours)[100]. Forty-three patients (23 female, 20 male) who have been diagnosed as acute ischemic stroke, in Neurology department of Ankara Hospital, between June 2001 and December 2001 were included in this study. He concluded that the fibrinogen and CRP have a close relationship as inflammatory markers in the acute phase of ischemic stroke. In this study, which supports the previous ones, it has been found out that CRP levels in the patient were higher than in the control group

levels. There was higher CRP level in the patients whose clinical health was poor and had high Stroke Severity Scale.

Another study conducted by Mitchell SV Elkind et al also showed that levels of hs-CRP are higher in stroke patients than in stroke-free subjects[101]. Levels of inflammatory biomarkers associated with atherosclerosis, including hs-CRP, appear to be stable for at least 28 days after first ischemic stroke This study also found an association of post-stroke levels of hs-CRP with smoking and stroke severity.

Muir KW et al in his study found that hs-CRP levels above 10.1mg/L when measured within 72 hours of stroke predicted mortality over 4 years[102]. Others found that the measurement of CRP at 24 or 48 hours, but not at admission, also predicted outcome[99]. In one study, hs-CRP levels $\geq$ 15 mg/L at discharge were associated with occurrence of a new vascular event or death at 1 year[96]. hs-CRP levels in the highest quintile measured at least 3 months after a first ischemic stroke or TIA were associated with an increased risk of subsequent stroke or MI in another study .

Another study was conducted by Yusuf Tamam et al to show the changes in plasma levels of six APPs (i.e., haptoglobin, ceruloplasmin, hs-CRP, fibrinogen, complement 3 and complement 4 during the first 10 days

after acute ischemic stroke. He concluded that the peak levels of APPs were higher in the AIS group than the control group ($p < 0.0001$)[1]. After stroke, hs-CRP, C3 and fibrinogen reached their highest values on the third day. The plasma levels of hs-CRP correlated positively with other five APPs studied ($p < 0.05$). His findings supported the importance of inflammatory processes after stroke. He suggested that the differences in levels of APPs could be used in predicting the outcome of ischemic stroke patient.

A population-based study of 476 people who had experienced their first ischemic stroke was undertaken to assess whether levels of lipoprotein-associated phospholipase A2 (LP-PLA2) and high sensitivity C-reactive protein could predict the risk of another stroke, vascular events, and death over the next 4 years[102]. During follow-up, people in the highest quartile of hs-CRP levels (≥ 31.2 mg/l) had double the risk of death after a stroke compared with people in the lowest quartile, but were no more likely to experience another stroke. Levels of hs-CRP were also significantly linked to initial stroke severity. Because stroke severity is also strongly associated with mortality after stroke they concluded that hs-CRP is also associated with mortality. Because levels of hs-CRP remained independently linked to mortality after accounting for stroke severity, they added that this marker may provide additional complementary prognostic information.

Elevated hs-CRP level are shown to be strongly associated with the extent of the atherosclerosis in the carotid arteries. The relationship between the increased serum hs-CRP levels and the atherosclerosis in the carotid arteries was found to be independent from the other known risk factors for the atherosclerosis.

Higher CRP concentration was an independent predictor of mortality together with age and the severity of the stroke on the National Institute of Health Stroke Scale (Muir K. W. *et al.*, 1999)[64]. In the same study, it was proposed that the CRP concentration was an independent predictor of the survival after the ischemic stroke which was consistent with the role of the inflammation in acute ischemic stroke, as well as with the hypothesis that elevated CRP might predict the future cardiovascular mortality. Other studies also showed the association between the increased levels of CRP with a worse outcome in patients with ischemic stroke[103] . Moreover in one study conducted in an elderly population without preexisting stroke, it has been demonstrated that elevated CRP concentration was an independent risk factor for future ischemic stroke over 10 years of follow-up[104] .

CRP formerly considered solely an excellent biomarker of inflammation, is now viewed as a direct contributor in atherosclerosis. Recent evidences have emerged implicating CRP directly in atherogenesis. CRP has

been found in human atherosclerotic plaque and CRP has been shown to cause endothelial cell dysfunction, oxidant stress and intimal hypertrophy in experimental models.

It must be stressed that CRP, because of its analytical and biological properties and the large amount of available data, is the only inflammatory marker accepted for clinical use. hs-CRP not only predicts future cardiovascular events but can also be used to target therapeutic interventions.

Levels of hs-CRP < 1, 1 -3 and >3 mg/L correspond to lower, moderate and higher risk of cardiovascular events at all levels of Framingham Risk Score and at all levels of metabolic syndrome.

MATERIALS AND METHODS

Setting:

Medical ward , Govt. Kilpauk Medical College, Chennai.

Study design:

Prospective hospital based study.

Period of study:

January 2008 to June 2008

Inclusion criteria:

1. All patients who presented within 48 hours of onset of stroke and who gave informed consent to participate in the study were included.

Exclusion criteria:

1. Subarachnoid haemorrhage, subdural haemorrhage and intracerebral haemorrhage were excluded with the aid of CT scan.
2. Patients above 70 years of age were excluded.
3. Patients with evidence of active infection and neoplastic conditions at the time of study were excluded.

4. Patients with rheumatic heart disease and collagen vascular disease were excluded.
5. Patients who were actively smoking at the time of study were excluded.
6. Patients with previous history of transient ischemic attack or reversible ischemic neurological deficit were excluded.

Study method:

A total of 50 patients who presented with acute ischemic stroke were enrolled into the study. That the stroke was an ischemic one was confirmed by CT scan. As soon as the patients were admitted within 48 hours of onset of stroke, serum samples were taken for hs-CRP estimation. Serum hs-CRP levels were also estimated in fifty normal patients (without any evidence of acute infection, neoplasm, rheumatic heart disease, collagen vascular disease, hypertension, DM, IHD) and was found to be within normal limits.

Standard guidelines for the treatment of acute ischemic stroke were followed. None of the patients received any thrombolytic treatment. They were treated only with antiedema measures and antiplatelets such as aspirin alone and with good nursing care and physiotherapy.

The patients were reviewed after 4 weeks after onset of stroke and were stratified using the Glasgow Outcome Scale (GOS). The serum hs-CRP level was correlated with the functional recovery of patients after 4 weeks using the GOS. Patients with score of 4 and 5 were included in the good outcome and patients with score of 1, 2, 3 were included in the poor outcome cateogory.

Definitions followed in the Study:

1. **Stroke**

Stroke (as defined by WHO) was defined as rapidly developing clinical signs of focal or global (for patients in coma) neurological deficit lasting more than 48 hours or leading to death with no apparent cause other than vascular origin.

2. hs-CRP:

Cut off value for hs-CRP for assessing the prognosis of stroke in this study was taken as $\geq$ 10.1 mg/L and the serum hs-CRP level was correlated with the functional recovery of patients after 4 weeks using the GOS. This was based on a study by Muir KW et al who found that hs-CRP levels above 10.1mg/L when measured within 72 hours of stroke predicted mortality over 4 years[102].

3. GOS:

The GOS was utilized to assess the functional outcome and residual neurological deficit. The GOS has frequently been used in trials involving stroke and brain injuries. It is a well validated scale with good interobserver agreement.

GLASGOW OUTCOME SCALE (GOS)[105,106]:

1 - indicates death

2 - a vegetative state (the patient is unable to interact with the environment)

3 - severe disability (the patient is unable to live independently but can follow commands)

4 - moderate disability (the patient is capable of living independently but unable to return to work or school)

5 - mild or no disability (the patient is able to to return to work or school)

Favourable outcome was defined as a score of 4 or 5 and unfavourable outcome as a score of 1, 2 , or 3.

4. Hypertension:

Hypertension in this study was taken as BP ≥ 140/90 mmHg as per JNC VII.

MEASUREMENT OF hs-CRP

The Quantia CRP-US (from Tulip Diagnostics Pvt. Ltd) was used for the measurement of hs-CRP. Quantia CRP is a turbidimetric immunoassay for ultrasensitive determination of CRP in human serum and is based on the principle of agglutination reaction . The test specimen is mixed with quantia CRP US latex reagent and activation buffer and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured at wavelength between 505-578 nm. The increase in turbidity corresponds to the concentration of CRP in the test specimen.

Test procedure:

400 microlitre of quantia CRP US activation buffer (R1) was pipetted out and added to 100 microlitre of Quantia CRP US latex reagent (R2) in the measuring cuvette. It was mixed well and incubated for 5 minutes. 5 microlitre of test specimen was added and mixed gently. Absorbance (A1)

was read exactly at 10 seconds and absorbance (A2) was read again at the end of exactly 4 minutes. ΔA (A2-A1) for test specimen was calculated. ΔA gives the CRP concentration ('C') of the test specimen.

The CRP concentration C was multiplied with the dilution factor (F) of the test specimen for obtaining the concentration of CRP in the test specimen.

Concentration of CRP in the test specimen in mg/dl=C x F,

(where F is the dilution factor of the test specimen)

The quantia CRP US reagent has been designed to measure CRP concentrations in the range of 0.015-1.0 mg/dl and is linear within the measuring range.

Statistical Analysis:

The statistical methods used for analysis were

1. Chi- Square test
2. Sensitivity/Speccificity test

All analysis were done using Windows-based SPSS stastistical package (Version 11.5).

RESULTS AND ANALYSIS

Total number of subjects included in the study = 50

Number of males =24(48%)

Number of females =26(52%)

Table 2: Age of individuals

	Number of Cases	Mean	SD	Std. Error Mean
Age	50	60.32	7.44350	1.05267

Mean age of individuals studied =60.32 yrs ± 7.44

Table 3: Time of sample collection

	Number of Cases	Mean	SD	Std. Error Mean
Time of collection	50	13.28	9.95713	1.40815

Mean time of sample collection was 13.28 hours ± 9.96

Table 4: CRP and S. Cholesterol levels

S.No	Marker	No. of cases	Mean	SD	Std. Error Mean	95% Confidence Interval of the difference	
						Lower	Upper
1.	S. Cholesterol	50	220.72	47.88935	6.77258	207.11	234.33
2.	S. hs-CRP	50	33.9023	31.56425	4.46386	24.9318	42.8728

Mean serum cholesterol level in these patients was 220.72 mg/dL

Mean hs-CRP level was 33.9023 mg/L

hs-CRP Vs Age group:

Out of the 14% of cases between the age group of 45-50 years, 2% had CRP values < 10.1 mg/L and 12% had CRP values ≥ 10.1 mg/L.

Out of the 12% of cases between the age group of 51-55 years , 6% had CRP values < 10.1 mg/L and 6% had CRP values ≥ 10.1 mg/L.

Between the age group of 56-60 years, 12% has CRP values < 10.1 mg/L and another 12% had CRP values than ≥ 10.1 mg/L.

Between the age group of 61-65 years, 2 cases (4%) has CRP values < 10 .1 mg / L and 8 cases (16%) had CRP ≥ 10.1 mg/L.

Between the age group of 66-70 years, 3 cases (6%) had CRP values < 10.1 mg /Land 12 cases (24%) had CRP values than ≥ 10.1 mg/L.

Table 5: hs-CRP vs Age group

Age group (yrs)	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
45-50	1(2%)	6(12%)	7(14%)
51-55	3(6%)	3(6%)	6(12%)
56-60	6(12%)	6(12%)	12(24%)
61-65	2(4%)	8(16%)	10(20%)
66-70	3(6%)	12(24%)	15(30%)
Total	15(30%)	35(70%)	50(100%)

P=0.245 NOT SIGNIFICANT

The correlation between age and hs-CRP levels was not statistically significant.

hs-CRP Vs Sex:

Out of the 24 males(48%) included in the study, 10% had CRP < 10.1 mg/L and 38% had CRP males had CRP ≥ 10.1 mg/L.

Out of the 26 females(52%) included in the study, 20% had CRP values < 10 .1 mg / Land 32% had CRP ≥ 10.1 mg/L.

Table 6: hs-CRP Vs Sex

Sex	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Male	5(10%)	19(38%)	24(48%)
Female	10(20%)	16(32%)	26(52%)
Total	15(30%)	35(70%)	50(100%)

P=0.174 NOT SIGNIFICANT

The correlation between sex and hs-CRP levels was not statistically significant.

hs-CRP Vs Smokers:

The CRP profile in both smokers and non-smokers was studied. 42% were smokers. Out of them, 8% had CRP values < 10.1 mg/L and 34% had CRP values ≥ 10.1 mg/L

Out of the 29 non smokers (58%), 22% had CRP values < 10.1 mg/L and 36% had CRP values ≥ 10.1mg/L.

Table 7: hs-CRP Vs Smokers

Smoker	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Yes	4(8%)	17(34%)	21(42%)
No	11(22%)	18(36%)	29(58%)
Total	15(30%)	35(70%)	50(100%)

P= 0.215 NOT SIGNIFICANT

The correlation between smokers and hs-CRP levels was not statistically significant.

hs-CRP Vs Alcoholics:

The hs-CRP profile of both alcoholics and non-alcoholics was studied. 38% were alcoholics . Among them, 8% had CRP < 10.1 mg/L. 30% had CRP ≥ 10.1 mg/L. Out of the 62% non-alcoholics in the study, 22% had CRP < 10.1 mg/L and 40% had CRP ≥ 10.1 mg/L.

Table 8: hs-CRP Vs Alcoholics

Alcoholic	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Yes	4(8%)	15(30%)	19(38%)
No	11(22%)	20(40%)	31(62%)
Total	15(30%)	35(70%)	50(100%)

P=0.351 NOT SIGNIFICANT

The correlation between alcoholics and hs-CRP levels was not statistically significant.

hs-CRP Vs Hypertension:

The CRP profile in hypertensives was studied. 60% were hypertensives in the study group. 10% had CRP < 10.1 mg/L and 50% had CRP values ≥ 10.1 mg/L.

Out of the 20 non-hypertensives(40%), 20% had CRP < 10.1 mg/L and another 20% had CRP ≥ 10.1 mg/L.

Table 9: hs-CRP Vs Hypertension

Hypertension	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Yes	5(10%)	25(50%)	30(60%)
No	10(20%)	10(20%)	20(40%)
Total	15(30%)	35(70%)	50(100%)

P=0.025 SIGNIFICANT

Thus the correlation between hs-CRP levels and hypertension was found to be statistically significant.

hs-CRP Vs Diabetics:

The CRP profile in both diabetics and non-diabetics was studied. 40% were diabetics in the study group. 8% had CRP values < 10.1 mg/L and 32% had CRP $\geq$ 10.1 mg/L.

Out of the 30 non-diabetics (60%), 22% had CRP < 10.1 mg/L and 38% had CRP $\geq$ 10.1 mg/L.

Table 10: hs-CRP Vs Diabetics

Diabetes	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Yes	4(8%)	16(32%)	20(40%)
No	11(22%)	19(38%)	30(60%)
Total	15(30%)	35(70%)	50(100%)

P=0.0345 NOT SIGNIFICANT

Thus the correlation between hs-CRP levels and diabetes was not statistically significant.

hs-CRP Vs IHD:

The CRP profile was studied among both IHD and non-IHD cases. 18% of the total cases were found to have IHD. Of that only 2% had CRP < 10.1 mg/L and 16% had CRP ≥ 10.1 mg/L.

Out of the remaining 82% non-IHD patients, 28% had CRP < 10.1 mg/L and 54% had CRP ≥ 10.1 mg/L.

Table 11: hs-CRP Vs IHD

IHD	hs-CRP (mg/L)		Total
	< 10.0	**≥10.1**	
Yes	1(2%)	8(16%)	9(18%)
No	14(28%)	27(54%)	41(82%)
Total	15(30%)	35(70%)	50(100%)

P=0.247 NOT SIGNIFICANT

Thus the correlation between hs-CRP levels and IHD was not statistically significant.

hs-CRP Vs GOS Score:

The serum hs-CRP levels were correlated with the functional outcome of the patient after 4 weeks with the help of Glasgow Outcome Scale (GOS).

All the patients with GOS score of 1, 2 and 3 (64%) had CRP values ≥ 10.1 mg/L. 4% in this study group died.

Out of the 20% with GOS score of 4, 14% had CRP < 10.1 mg/L and 6% had CRP ≥ 10.1 mg/L.

All the 16% cases with GOS score of 5 had CRP levels < 10.1 mg/L.

Table 12: hs-CRP Vs GOS Score

GOS	hs-CRP (mg/L)		Total
	< 10.1	**≥10.1**	
1	0(0%)	2(4%)	2(4%)
2	0(0%)	13(26%)	13(26%)
3	0(0%)	17(34%)	17(34%)
4	7(14%)	3(6%)	10(20%)
5	8(16%)	0(0%)	8(16%)
Total	15(30%)	35(70%)	50(100%)

hs-CRP Vs GOS Group:

Out of the 34% cases with GOS score of 4 or 5, i.e those with favourable outcome, 30% had CRP < 10.1 mg/L and 4% had CRP ≥ 10.1 mg/L.

All the remaining 66% cases with GOS score of 1, 2 or 3, (i.e unfavourable outcome) had hs-CRP ≥ 10.1 mg/L.

Table 13: hs-CRP Vs GOS Group

GOS group	hs-CRP (mg/L)		Total
	< 10.1	**≥ 10.1**	
Favourable	15(30%)	2(4%)	17(34%)
Unfavourable	0(0%)	33(66%)	33(66%)
Total	15(30%)	35(70%)	50(100%)

P= 0.000 SIGNIFICANT

Thus there was significant statistical correlation between hs-CRP levels and functional outcome of the patient at the end of 4 weeks based on GOS score.

SENSITIVITY/ SPECIFICITY TEST FOR hs-CRP:

Table 14: Sensitivity/ Specificity Test for hs-CRP

Parameter	Estimate	Lower - Upper 95% CIs
Sensitivity	100%	(89.57, 100)
Specificity	88.24%	(65.66, 96.71)
Positive Predictive Value	94.29%	(81.39, 98.42)
Negative Predictive Value	100%	(79.61, 100)
Diagnostic Accuracy	96%	(86.54, 98.9)

Thus hs-CRP is 100% sensitive and 88.24% specific as a prognostic tool in acute ischemic stroke. hs-CRP has a diagnostic accuracy of 96% in patients with acute ischemic stroke.

DISCUSSION

The correlation between hs-CRP levels measured within 48 hours of onset of stroke to that of the functional outcome of the patient at the end of 4 weeks (using GOS) was carried out.

Out of the 50 cases enrolled in the study, 35 cases (70%) had CRP values $\geq$ 10.1 mg/L and 15 cases (30%) had CRP < 10.1 mg/L.

Out of the 35 cases with CRP $\geq$ 10.1 mg/L, 4% had GOS score of 1, 26% cases had GOS score of 2, 34% cases had GOS score of 3.

On the other hand, of the remaining 15 cases with CRP < 10.1 mg/L, none had a GOS score of 1, 2 or 3. 14% cases had a GOS score of 4 and 16% cases had a GOS score of 5.

Out of the 50 patients, 2 died. Both of them had very high hs-CRP levels. Thus patients with CRP levels < 10.1 mg/L had a relatively favourable outcome (GOS score of 1, 2 or 3) when compared to patients with levels $\geq$ 10.1 mg/L (GOS score of 4 and 5).

So, in our study, the correlation between hs-CRP levels within 48 hours of onset of ischemic stroke and the prognosis of the cases at the end of 4 weeks was statistically significant, the p value for hs-CRP being 0.000.

This is consistent with the various studies conducted using hs-CRP as a prognostic indicator of acute ischemic stroke.

Table 15: Studies conducted using hs-CRP as a prognostic indicator

S. No	Study	Year
1.	Di Napoli[4,78,96]	2001, 2002, 2005
2.	Yusuf Tamam et al[1]	2005
3.	Muir KW, Weir CJ, Alwar W et al[64]	1999
4.	Mitchell S V Elkind et al[101]	2006
5.	Ufuk Emre et al[100]	2007
6.	Winbeck K et al[99]	2002
7.	Kocer A et al[98]	2005
8.	Rost N S et al[103]	2001
9.	Cao J J et al[104]	2003

The correlation of hs-CRP levels with age and gender was studied. There was no statistically significant correlation between age and gender of the patient with the hs-CRP levels. This may be because of the small sample

size of our study group. But in a study conducted by So Yeon Ryu et al[82] in 2005, age had an independent association with plasma hs-CRP whereas gender showed no significant association with plasma hs-CRP. Also another study conducted by Rohde Lep et al[81] in 1999 concluded that hs-CRP levels were statistically significant with age, number of cigarettes smoked per day, BP, total cholesterol.

In our study, smoking and alcohol had no statistical significance with hs-CRP levels. This is in contrast to a study conducted by So Yeon Ryu et al[82] in 2005, where smoking had a significant correlation with plasma hs-CRP levels. Smoking is well supposed to give chemical and oxidative stimuli to the cardiovascular system and cause inflammation. The same study also reported that moderate alcohol consumption reduces circulating hs-CRP. Moderate alcohol consumption has anti-inflammatory effects. The mechanism causing moderate alcohol to decrease CRP levels needs further investigation. It involves nuclear factor (NF) – κB (Blanco – Colio et al 2000)[107]. NF-κB is a redox sensitive transcription factor which activates geans involved in the immune, inflammatory or acute phase response, such as cytokines IL – 6[68] and TNF - α[83] which regulates CRP production by liver. Another study conducted by M. Averina et al[92] in 2003 and Chrysohoou et

al[93] in 2003 showed a U-shaped association between hs-CRP and total alcohol intake.

In our study, total serum cholesterol did not have statistically significant correlation with hs-CRP levels. This is in contrast to a study conducted by So Yeon Ryu et al[82] in 2005. A limitation of our study was that only total serum cholesterol was estimated and not the complete lipid profile.

Our study showed a statistically significant correlation between high BP and hs-CRP. This is consistent with the study conducted by So Yeon Ryu et al[82] in 2005 and Blackburn R et al[88] in 2001.

Diabetes had no statistical significance with hs-CRP in our study. This is in contrast to many of the previous studies. This may be because of the small sample size and also because of the fact that our study included only acute ischemic stroke patients; it was not done exclusively on diabetic subjects.

Table 16: Studies showing significant correlation between hs-CRP levels and DM

S.No	Study	Year
1.	Blackburn R. et al[88]	2001
2.	Minna Soinio et al[95]	2006
3.	So Yeon Ryu et al[82]	2005

Our study also did not show a statistically significant correlation between IHD and hs-CRP levels. This is in contrast to many of the previous studies. This may be because our study included only ischemic stroke patients, it did not include IHD cases without stroke.

Table 17: Studies showing significant correlation between hs-CRP levels and IHD

S.No	Study	Year
1	Liuzzo et al[21]	1994
2	Ferreiros et al[27]	1999
3	winter et al[26]	1999
4	Rasouli Mehdi et al[94]	2006

The major difference between our study and those of other studies mentioned above was that our study involved only hs-CRP levels and not other acute phase reactants like fibrinogens. Also, in our study we assessed the outcome of patients with acute ischemic stroke at the end of four weeks and not at the end of one year. Also, we measured the CRP levels only within 48 after the onset of ischemic stroke and not at the end of four weeks or at the time of discharge. This was because of the cost involved in the measurement of hs-CRP. The other reason, why our study did not have significant correlation with age, sex, DM, IHD was that our study sample size was very small.

The prognostic importance of the 48-hour concentration of CRP may be partly related to the extent of ischemic necrosis and partly to the unknown individual determinants of the intensity of the acute phase reactants. CRP is a very vital indicator of the inflammatory states during the acute phase of an ischemic stroke.

Knowledge of the prognostic influence of the levels of CRP in the outcome of stroke of atherothrombotic etiology helps the clinician to offer realistic expectations to the families of stroke victims.

Thus, CRP can be routinely measured for all stroke patients , as it has been found to provide a statistically significant level of prognostic information as to the eventual outcome of stroke both in short term such as in our study and also over a longterm as was shown in the study by DiNapoli - et-al [4,78,96].

Also, CRP has a direct relationship with other cardiovascular risk factors, like smoking, alcohol consumption, hypertension, diabetes and cholesterol. Thus CRP levels may be a marker for preclinical cardiovascular disease.

As CRP was found to be an independent risk indicator of further cardiovascular and neurovascular events as shown by the subset of Framingham study, routine CRP screening of susceptible population like chronic smokers and sibilings and first degree relatives of patients with IHD and stroke may prove a valuable indicator for predicting future athreothrombotic events and then it can be assessed as a routine indicator for aspirin prophylaxis. Thus CRP measurements may be helpful in grading patients into high risk and low risk category for predicting future cardiovascular and neurovascular events.

CONCLUSION

- Patients with elevated hs-CRP had a poorer outcome when compared to patients with lower levels of CRP, four weeks after the onset of ischemic stroke.

- hs-CRP levels showed statistically significant elevation in patients with high blood pressure.

- hs-CRP levels had no significant correlation with age or gender.

- hs-CRP did not show a statistically significant correlation with smoking or cholesterol intake.

- There was no statistically significant correlation between hs-CRP levels and those with diabetes or IHD.

SUMMARY

This study was done to evaluate the predictive value of hs - CRP in relation to the ultimate functional outcome in first ever ischemic stroke after 4 weeks and also to correlate the hs - CRP levels with various cardiovasclar risk factors. It was found that patients with elevated hs - CRP levels had a poorer outcome when compared to patients lower levels of hs - CRP, 4 weeks after the onset of ischemic stroke. This study also showed that hs - CRP levels were elevated in patients with high B.P.

Thus routine screening of susceptible populations like chronic smokers, alcoholics and first degree relatives of patients with IHD, stroke and DM may prove a valuable indicator for predicting future cardiovascular and neurovascular events.

Thus hs - CRP measurements may be helpful in grading the patients into high risk and low risk category, for predicting future adverse atherothrombotic events and outcome.

ABBREVIATIONS

%	-	Percentage
APP	-	Acute phase protein
BP	-	Blood pressure
CAHD	-	Coronary artery heart disease
CHD	-	Coronary heart disease
CI	-	Confidence Interval
CRP-US	-	C-Reactive Protein ultra sensitive
DM	-	Diabetes mellitus
Gp	-	Group
hs-CRP	-	High sensitivity C-Reactive Protein
HT	-	Hypertension
IHD	-	Ischemic heart disease
IL	-	Interleukin
JNC	-	Joint National Committee
mg/L	-	Milligram/litre
MI	-	Myocardial infarction
m-RNA	-	Messenger – RNA
OCP	-	Oral contraceptive pill
SAA	-	Serum amyloid A
SAH	-	Subarachnoid haemorrhage
SD	-	Standard deviation
TIA	-	Transient ischemic attack
yrs	-	Years

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PROFORMA

Name: IP No: Serial No:

Age:

Sex:

Occupation:

Address:

Smoking:

Alcohol:

DM:

HT:

IHD:

ClINICAL EXAMINATION:

Pulse rate: BP:

CVS:

RS:

Abdomen:

CNS:

GOS after 4 weeks:

INVESTIGATIONS:

Hb%:

Total count:

Differential count P- , L- , E- , M- , B-

ESR:

hs-CRP:

Blood urea:

Blood sugar:

Serum creatinine:

Serum electrolytes:

Serum cholesterol:

ECG:

CXR-PA view:

CT brain: